SCIENCE NEWS of the week

New Gene Ties Cancer, Cell Cycle

Three research groups seeking genes in different ways for very different reasons have discovered one that helps explain the development of cancer. The gene, which goes by at least three names, leads to the production of a protein that keeps cells in a resting, nondividing stage of the cell cycle. It is regulated by a tumor suppressor gene, called p53, already known to be important in keeping some cells from forming tumors (SN: 6/5/93, p.356).

"[The gene] is a missing piece [that explains] a lot of things that we didn't understand before," says James R. Smith of Baylor College of Medicine in Houston.

The new results indicate that when p53 fails to do its job, the cell stops making this new gene's protein, setting the stage for cancer. "[The results] provide a direct link between a tumor suppressor protein and the cell cycle," comments Tony Hunter, a molecular biologist at the Salk Institute in La Jolla, Calif.

Figuring out how p53 regulated the cell cycle "was sort of the Holy Grail in the tumor suppressor field," adds J. Wade Harper, a Baylor biochemist.

Smith and his colleagues had wanted to understand why old cells lose their ability to divide. They inserted pieces of DNA derived from nondividing, senescent cells into young cells that were rapidly dividing in a laboratory dish and monitored which DNA stopped cell division.

Three DNA strands had this effect on the cells. The researchers isolated a gene from the strand most active in older cells, naming it senescent-cell-derived DNA inhibitor 1 (SDI-1) because it interfered with the synthesis of new DNA. The team will report its results in an upcoming EXPERIMENTAL CELL RESEARCH.

SDI-1 turned out to be the same gene that Harper and his colleagues, located just one floor away, had uncovered while investigating genetic regulation of the cell cycle. That group had called the gene CIP1. Then a casual phone conversation between Baylor's Stephen J. Elledge and Bert Vogelstein of Johns Hopkins School of Medicine in Baltimore led to the realization that Vogelstein's team also had this gene in hand, under the alias of WAF1.

"We were the first two people to have a model of how p53 worked," Elledge recalls. "It was really quite a moment when we figured this out."

Vogelstein had known that the p53 protein exerts its tumor-suppressing effect indirectly, by regulating the activity of other genes. Using brain tumor cells grown in a laboratory dish, he and his colleagues determined that WAF1 turned on in the presence of normal p53 genes but not in the presence of mutant p53, they report in the Nov. 19 CELL.

The addition of lots of WAF1 to brain, lung, and colon tumor cells lacking functional p53 stops the cells' uncontrolled growth, notes Hopkins' Watik S. El-Deiry. Also, their data show that human p53 activates rodent WAF1, demonstrating that these genes and their proteins have been conserved through evolution.

While the Hopkins group was figuring out how p53 works, Harper and Elledge were trying to understand the link between the cell cycle and cancer. They developed a screening test to determine what controlled the activity of a cyclin-dependent kinase enzyme. This enzyme and others like it link up with proteins called cyclins, and together these molecules push a cell to start dividing.

The researchers screened for CIP1 by adding different pieces of human DNA to genetically engineered yeast. Genes essential for the yeast's survival would turn on only when the added DNA caused the yeast to produce a protein that bound to cyclin-dependent kinase, also a protein. Other work had already implicated the CIP1 protein in cell division.

The discovery illustrates the power of this new screening technique, which enables scientists to elucidate protein-protein interactions, says Elledge.

Next, Harper and Elledge determined that in a laboratory dish, CIP1 virtually shut down the chemical activity of the cyclin-dependent kinase. Further tests showed that the CIP1 protein did not keep the kinase from attaching to cyclin but did make the pair ineffective in stimulating cell division, they report in the Nov. 19 CELL.

Cells typically possess this built-in check on cell division. But when p53 malfunctions, "the cell can no longer make sufficient levels of the inhibitor to stop the cell cycle," Harper suggests.

"I think this idea of negative regulators is going to be an important one," says Hunter. However, he and the Hopkins group caution that this gene and its protein, whatever its name, may not be the critical target or may be just one of several targets of p53 and other regulators of cell division.

Even so, these scientists say they hope the discovery will lead to new anticancer therapies. — *E. Pennisi*

Dioxin linked to reproductive disorder

For the first time, researchers have connected the chemical TCDD, one of the most toxic members of the dioxin family, to endometriosis, a painful disease that affects an estimated 10 percent of women and can cause reproductive problems.

In a study of rhesus monkeys exposed to TCDD, Sherry E. Rier of the University of South Florida College of Medicine in Tampa and her colleagues found that TCDD's effects on the body's hormonal and immune systems (SN: 1/11/92, p.24) may underlie the endometriosis-dioxin link, she says. "Chronic immunosuppression in combination with hormonal dysregulation may have facilitated the aberrant growth of endometrial tissue" in the monkeys, the team writes in the November FUNDAMENTAL AND APPLIED TOXICOLOGY.

In endometriosis, endometrial cells grow outside their usual home in the uterus, forming nodules in such places as the fallopian tubes or ovaries.

The study is "strongly supportive" of a link between TCDD exposure and the disease, says Linda S. Birnbaum, director of environmental toxicology at the Environmental Protection Agency in Research Triangle Park, N.C.

Endometriosis had been found in rhesus monkeys exposed to polychlorinated biphenyls (PCBs) and to radiation. TCDD, however, had not been implicated.

For four years beginning in 1978, Rier's group fed 14 monkeys a TCDD-laced diet as part of a study on the health effects of that chemical. Autopsies on three monkeys that died between 1990 and 1992 uncovered endometriosis and prompted the researchers to examine the other animals.

The team found that five of the seven animals that had received a large dose of the chemical — 25 parts of TCDD per trillion parts of food (ppt) — developed moderate to severe endometriosis. Three of the seven given 5 ppt of TCDD had moderate to severe disease. Other monkeys, including two of six fed a normal diet, developed a very mild form of the disease.

Stores of TCDD peaked at 100 to 800 parts per trillion in the body fat of the monkeys, says Robert E. Bowman, a retired behavioral toxicologist and member of the study team. However, people and animals vary considerably in how much dioxin they store, he warns. At about 100 ppt of TCDD, monkeys "are getting into dangerous territory" regarding the risk of endometriosis, he says. The body fat of most humans contains about 7 ppt of TCDD, says Bowman. — *T. Adler*